THE PATHOLOGICAL ANATOMY OF BRONCHIAL ASTHMA.

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Owing partly to lack of definite knowledge regarding the pathological anatomy of bronchial asthma, various theories have been advanced concerning its nature. The explanations given by different clinicians may be placed in three groups:

1. *Spasm of the Diaphragm.* First propounded by Wintrich, this theory has been supported by a number of later writers. Riegel and Edinger[1] conclude that spasm of the diaphragm, more than spasm of bronchial muscles, plays an important part in asthmatic attacks. Their opinion was based on experimental studies, and possibly is entitled to more than usual attention, because they had fully expected to prove exactly the opposite. More recent writers are in general not favorably inclined toward this view.

2. *Spasm of the Bronchial Muscles.* This view of Biermer's[2] still has many adherents, some holding it to be the principal feature, others at least a part of the asthmatic phenomenon. Riegel and Edinger state that their own and other experiments indicate with certainty that the smooth muscle fibers of bronchi contract upon irritation of the vagi; that this is the cause of asthma, however, is not proved. Their view that this is less important than spasm of the diaphragm has been mentioned. Lazarus,[3] from experiments on rabbits, concludes that both bronchospasm and asthmatic catarrh are necessary to produce bronchial asthma. Talma[4] regards the affection as primarily due to spasm of the muscles of the respiratory tract. These muscles are, to a certain extent, under control of the will, or can be brought under control, hence his method of treating the disease by respiratory gymnastics. Aufrecht[5] convinced himself that the musculature of the finer bronchi consists (as in animals) of a stout layer of circular and a much weaker layer of longitudinal fibers, the effect of the contraction of which is evident. Nevertheless, he does not admit that asthma must be regarded as a consequence of bronchial muscle cramp, since the affection may be due to catarrh of the finer bronchi.

[1] Ztschr. f. klin. Med., 1882, v, p. 413.
[2] Volkmann's Samml. klin. Vorträge, 1870, Nr. 3.
[3] Deut. med. Woch., 1891, Nr. 27, p. 852, and Nr. 36, p. 1057.
[4] Berl. klin. Woch., 1898, Nr. 52, p. 1141.
[5] Deut. Archiv f. klin. Med., 1900, Band lxvii, p. 586.

Fraenkel[6] says the theory of bronchial muscle cramp explains, for the most part, the phenomena of the asthmatic attack, and experimental physiological investigations regarding contractility of the bronchi give this some support. These investigations, however, give too little consideration to undoubted changes in the bronchial mucous membrane. Elsewhere, in discussing the mechanism of spiral formation, he assigns a necessary function to bronchial spasm, stating that, in addition to the tenacity of the bronchial secretion, at least an indirect part is taken by such contraction. The latter, narrowing the bronchial lumen, has to do with consistence of the mucus, and interferes with the passage of air. When this spasm fails, as in ordinary asthma, tenacious sputum alone is not formed into spirals.

Pieniazek[7] regards the view that attacks of bronchial asthma are due to cramp of small bronchi as not tenable; much more probably are they due to swelling of the mucous membrane in the smaller bronchi. Grossmann[8] says the power of contractility of the bronchial muscles can be no longer denied. This is, however, by no means strong enough in itself to produce a grave respiratory disturbance. Experimentally it is not possible to produce contractions of the bronchi without at the same time causing circulatory changes in the pulmonary vessels. Clinically, doubtless these two conditions always run parallel. On the other hand, changes in the pulmonary circulation can, experimentally as well as clinically, appear without contraction of the muscles. Upon the degree and rapidity of onset and disappearance of this circulatory change depend also the degree and acuity of the respiratory disturbance.

3. *Bronchial Catarrh.* That this condition forms a large, if not indeed the principal, part of the pathology of bronchial asthma is believed by many observers, some of whom have been quoted in the preceding paragraphs. Fraenkel says that mere catarrh of the finer air passages is to be rejected as the only cause of asthma, because it furnishes no basis for the suddenness of the attacks. It is doubtful if in all cases catarrh goes before spasm of the muscles, although it appears plausible that spasm of muscles might easily follow when bronchioles are partly closed by swelling of the mucosa and the presence of tenacious content. Pieniazek, in upholding this theory, states that swelling of the mucous membrane can occur very quickly, as is seen in cases of œdema of the uvula, in urticaria, etc. Retardation of expiration is better explained by this than by muscle cramp. Pathologically he regards asthma as standing between pure œdema and acute catarrh. To paralysis of the small bronchial veins he assigns the swelling of the mucous membrane.

[6] Spezielle Pathologie u. Therapie der Lungenkrankheiten, 1904.
[7] Wien. klin. Woch., 1905, Nr. 46, p. 1201.
[8] Ztschr. f. klin. Med., 1907, Band lxii, p. 179.

Aufrecht believes that asthmatic attacks of a day and longer are better explained by assuming the presence of catarrh.

Whatever the changes in the bronchi, or the diaphragm, may be, they apparently are the result of a primary disturbance in the nervous system. Hoffmann[9] states that by asthma we understand a neurosis in the domain of the respiratory nerves, which shows itself by attacks of dyspnœa, with characteristic secretion and distention of the lungs; the affection is, perhaps, a pathological change in the respiratory centre of the medulla. Fraenkel's view is that the asthmatic patient has to charge for the greater part, probably even exclusively, the peculiar condition of his nervous system as the source of his disease. In the majority of instances this condition is a hypersusceptibility of that portion of the nervous system which is in direct relation to the respiratory tract. In a series of cases the responsible focus is a circumscribed area which, through gradual pathological changes, becomes an irritation point, from which attacks develop, as in many forms of nasal asthma. In a second type there is increased irritability of the collective mucous surface from the nose to the bronchi, and in a third there possibly exists a similar condition in the bulbar respiratory centre. Finally, in a minority of cases, the remainder of the nervous system may be at fault, as in asthma, which is one of the phenomena of general neurasthenia. With right, therefore, he says, asthma may be designated a reflex neurosis.

Materials from which to determine the pathology of asthma are principally two—the sputum ejected by persons suffering from the disease, and the lungs of those who die during an attack. The former, largely a clinical question, about which a great deal has been written, I shall later discuss briefly in connection with certain points relating to lesions found in the lungs. As regards the latter, I have found in literature the reports of but seven cases in which histological studies were made of the lungs of asthmatic subjects who died during an attack of that disease. The findings in these may be thus briefly summarized:

CASE I (von Leyden[10]).—Female, aged forty years. From childhood had almost daily attacks of asthma. Died in an attack during cyanosis, dyspnœa, and stertor. At autopsy a high grade vesicular emphysema of both lungs was found. The bronchi were not dilated; the mucosa was reddened, but not otherwise abnormal. Microscopically some of the alveoli were dilated; others were not. They were filled with granular material in which was embedded a moderate number of large cells. In the smaller bronchi was a similar material tightly adherent to the walls and narrowing the lumina; at one point this substance formed a plug-like mass that

[9] Nothnagel, Spec. Path. u. Ther., Band xiii.
[10] Deut. Militärärztl. Ztschr., 1886, Heft ii.

completely occluded the bronchus. Neither fibrin nor Charcot-Leyden crystals were found in this mucous material occupying the bronchi. The walls of the bronchi were not essentially changed.

CASE II (Berkart[11]).—Female, aged thirty-seven years, who had suffered from attacks of asthma during a period of fourteen years, finally dying in a state of dyspnœa and general congestion. Autopsy showed hypertrophy and dilatation of the heart and emphysema of the lungs. In the right primary bronchus was a dark brown clot-like plug, almost closing the lumen; a similar mass was in a branch of the left bronchus. Many of the smaller bronchi were not only dilated, but were also partly occluded by exudate. Microscopically the epithelium was absent from the wall of the right bronchus over the area in contact with the plug, and also from the smaller bronchi, where there was an ostensible fibrinous exudate. The medium sized bronchi were more or less nearly filled by detritus-like masses, in which were fragments of Charcot-Leyden crystals. The brownish clot in the right bronchus consisted chiefly of degenerated epithelium in connection with spirals. Among the epithelium were cylindrical types which showed change into thread-like forms of variable length, some of these appearing as whip-like projections on fairly well preserved cells. Similar long-drawn-out cells had also been found in the sputum. A part of the emphysematous pulmonary alveoli contained fibrinous exudate.

CASE III (Schmidt[12]).—Female, aged forty-nine years, who had developed asthma in addition to a medullary carcinoma of one lung. Patient died during a severe exacerbation of an attack lasting a week. Section of the lungs showed that the peripheral somewhat dilated bronchi of the upper lobe of each were surrounded by grayish pigmented, strongly compressed tissue here and there beset with caseous foci. They contained spiral-formed mucous threads, which were unusually adherent to the walls, but could by forceps be drawn out in masses many centimeters long. Microscopic examination showed that in the majority of the small dilated bronchi the epithelium was well preserved. By the application of various staining methods (Weigert's thionin, triacid) it was clearly demonstrated that the content was, for the greater part, mucus, with a few cellular elements and Curschmann's spirals. The spirals diminished toward the periphery, and only in certain places could a turned appearance of the content in the respiratory bronchioles be noted. Nowhere in the considerably dilated alveoli could a spiral be found. The mucosa and submucosa were infiltrated by round cells. For the greater part the lumina were entirely filled with a homogeneous material in which were embedded, in addition to spirals, various types of cells. These included alveolar epithe-

[11] On Bronchial Asthma, 1889, 2d edit.
[12] Ztschr. f. klin. Med., 1892, Band xx, p. 476.

lium, a moderate number of leukocytes with lobed nuclei (but none with eosinopbile granules), bomogeneous, round, oval, or spindle cells, witb neither nuclei nor granules, and epithelial cells, sometimes in masses. The content of the ducts of the mucous glands showed no especial consistence or winding, though the glands were in strong secretion. As typical central threads were found also in the smaller glandless bronchi, it was evident that they were a secretory product of neither the mucous glands nor their ducts. Surrounding the mucus-filled bronchi were areas of considerable alveolar dilatation; these alveoli contained a slight amount of granular material or were entirely filled with a substance resembling that in the bronchi and shown by thionin and triacid to be mucus. The bronchi containing no mucus were empty or contained cells the larger number of which were polynuclear leukocytes. Surrounding the latter bronchi were bronchopneumonic areas; that is, the septa were infiltrated, the alveoli were emphysematous, and in them were many alveolar epithelial cells and leukocytes without intercellular material.

CASE IV (Fraenkel[13]).—A man aged sixty-three years, who, during his last year, had many attacks of asthma. At autopsy both lungs were found widely expanded, meeting in the middle line. In the left primary bronchus was a large quantity of thin mucous fluid. The lung was largely air-containing, and on the border were many cherry-sized emphysematous vesicles. The bronchial mucous membrane was strongly reddened, the lumina were dilated, and in part filled with tough masses which could be pulled out in the form of thready clots. The right lung possessed extensive adhesions, and the cut surfaces showed marked œdema. The bronchi were widened and contained material similar to that in the left. The walls of the larger bronchi were thickened and at points showed scars and lime deposits. The bronchial glands were large and pigmented.

In stained sections from the bronchial clots typical large spirals were not seen, but instead a large number of thready, in part wound, formations, staining blue, and not entirely homogeneous, but slightly granular in appearance (fibrin?). Other similarly formed clots consisted of cylindrical epithelium, in part close together, in part irregularly placed, in part palisade-like, as before desquamation. In a few was a suggestion of winding. Eosinophiles were not perceptible.

Microscopic examination of the tissue showed a high-grade desquamative bronchial catarrh. The cylindrical epithelium was detached and filled the lumina, being in part in serpentine form, in part as distinct bands around a central axis. These cell accumulations were in some places so great as to fill the bronchial

[13] Ztschr. f. klin. Med., 1898, Band xxxv, p. 559.

lumen. The vessels of the mucous membrane were dilated, the peribronchial tissues infiltrated with small cells. In consequence the denuded mucous membrane was at points elevated, and the bronchial wall appeared not inconsiderably thickened. The lung was in part normal, in part emphysematous, with, at points, increase of interstitial and interalveolar tissues. In many places alveoli were filled with blood, and in others, in the vicinity of dilated bronchi, the lumina and walls were so filled with lymph cells as almost to arouse the impression of beginning suppuration. At other points the lungs showed atelectasis, partly due to dilatation of bronchi, partly to increase of connective tissue.

CASE V (Fraenkel[14]).—A woman, aged forty-eight years, who, at various times, suffered from asthma, during the last period being under observation for more than a year. Attacks occurred almost daily. The tenacious sputum contained numerous coagula, with Curschmann's spirals and asthma crystals therein. The last typical attack occurred thirty-six hours before death. In spite of this the majority of middle-sized and small bronchi were found at autopsy to be filled with exquisite screw-shaped coagula, some many centimeters in length. Sections of the lung were stained by a modification of the Biondi-Heidenhain method, and showed, as did Schmidt's, that the bronchial effusion was entirely of mucus. In many of the dilated small bronchi were spiral figures whose centres stained the same as the mucous cell content of the epithelium lining the tube, while the mesh-like spaces of the periphery contained numerous eosinophiles.

The genesis of the coagula in the small bronchi of 0.15 to 0.3 mm. lumen could be distinctly followed. First was a considerable increase in the ciliated cells of the epithelial covering, of which isolated cells throughout were very much longer than the normal, the transverse diameter being correspondingly diminished. Some cells were 20 microns high. The nuclei were still normal. Mucus protruded from the cell bodies and into the lumina of the bronchioles or passed over directly into spirals. At many points, in some over the entire circumference, numerous large epithelial cells were loose and so far from the wall that three or four lay behind each other. These free cells were drawn out, in part large spindle-formed, and showed on the end toward the bronchial wall whip- or awl-like thin projections, which lost themselves between the cells that were not so greatly changed and were still attached to the wall. Other changes in the bronchi were hyperemia of the mucous membrane, with small blood extravasations, and the specially striking appearance of numerous heaps of closely placed leukocytes in the thickened walls of the bronchioles. These cells were largely eosinophiles, of which the majority were mononuclear, similar to

[14] Deut. med. Woch., 1900, Nr. 17, p. 269.

those already mentioned as in the lumina of the bronchi. In the immediate vicinity of the eosinopbiles, and in part surrounded by them, were groups of well-formed Charcot-Leyden crystals.

CASE VI (Jezierski[15]).—A man aged sixty-three years, whose father also died of asthma. Had first attack in 1900, followed by others in 1903 and 1904. Died of right-sided pneumonia in two days while under treatment for asthma. At autopsy the right lung was large and heavy, the middle and upper lobes liver-like in consistence. The left lung was small, light, slightly pigmented; the bronchi were dilated, their mucosa red. The cut surfaces of the right upper lobe were dark red and covered with foamy fluid; of the middle lobe, grayish yellow to red, and with protruding granules. Isolated, many-branched fibrin plugs were in the small bronchi. Material saved for microscopic study included medium and smaller bronchi of the left lung, pieces of the right lung, diaphragm, and both phrenic and vagi nerves.

Microscopically the bronchioles showed in the lumina closely crowded cell masses in addition to well-preserved cells, chiefly ciliated epithelium, which singly or in rows had desquamated or remained hanging to the basement membrane by long thin stalks; among them were also round, non-ciliated epithelium, numerous leukocytes, lymphocytes, erythrocytes, and eosinophiles, all embedded in a ground substance which was shown to be mucus. Fibrin was not demonstrated. At the basement membrane the epithelium was well preserved, though between the elements were round cells. The latter were also numerous in the walls and peribronchial tissues, some diffusely placed, some in heaps, arranged in part like lymph nodes. The quantity of elastic tissue was unusual, far exceeding that in the lungs of other individuals of the same age, and of arteriosclerotic persons, with which they were compared. Also unusual was the presence in the bronchial walls of an abundance of small bloodvessels. On transverse section of the bronchi these vessels appeared closely crowded together, forming, as it were, a palisade-like wall around the tunica propria. In some of the vessels were isolated fibrin threads. In the perivascular lymph spaces were numerous cocci, mainly diplococci; these were also found sparsely in the lumina of the bronchioles. The peribronchial tissues were likewise infiltrated by round and blood cells. Study of the diaphragm and the neck muscles showed rarification and fatty infiltration of the former; otherwise nothing abnormal. The vagi and small nerves of the neck were intact. The phrenic nerves showed, by Marchi and Flemming safranin staining methods, some changes, a part of the fibers being tinged blackish brown, or swollen or notched in a bead-like manner. The right lung showed a typical pneumonic condition.

[15] Deut. Archiv f. klin. Med., 1905, Band lxxxv, p. 342.

CASE VII (Jezierski).—Female, aged forty-six years, who had attacks of asthma for twelve years, death from dyspnœa occurring during an attack. In each pleura was, approximately, 200 c.c. of bloody serum. The left lung was markedly emphysematous, but on section showed a good blood content. On pressure there flowed from some bronchi small, worm-shaped, quite consistent mucous masses. The right lung on section showed somewhat smaller worm-shaped structures, but otherwise was like the left. Small pieces of these clots examined fresh showed an enormous quantity of epithelium, mostly ciliated, with long clear nuclei and heavy cilia. The majority were striking because of their unusual narrowness and length, especially the end threads, which often reached one-third the diameter of the field ($\frac{1}{12}$ oil immersion), as already described by Berkart and Fraenkel. In addition was cuboidal epithelium from the deeper layers, numerous round cells, isolated red cells, and masses of detritus. In sections of the clots the nuclear structure and narrowness of the thread-formed epithelial cells did not show so clearly; there appeared here numerous eosinophiles, round and polygonal epithelium, many with two nuclei, pale, barely tingible cell remains, and, as ground substance, mucus.

The bronchi, on transverse and longitudinal section, showed mostly intact and undamaged epithelium. Only in isolated places was it detached or broken through by masses of round cells. These penetrated between the epithelial cells as rows, passed into the basement membrane, and infiltrated widely the bronchial walls and peribronchial tissues, either diffusely or in isolated masses. In part they were small, mononuclear, with scanty protoplasm, but the majority were larger, with dark, indented nuclei and abundant protoplasm; they were most numerous in the vicinity of vessels. The smaller the bronchus the more numerous were the cells, often so many in the lumen and surrounding tissues that the bronchial structure was not clear. The elastic tissue was in this case not increased, neither was there the new vessel formation as in the first. The pulmonary parenchyma was intact.

Through the courtesy of Professor Dr. Stadelmann, Director of the Department of Internal Diseases, and of Dr. Pick, Prosector of the Friedrichshain Hospital, I am enabled to add to this list another case. To both these gentlemen, and especially to Dr. Pick, for his kind supervision of my work, I hereby express my warmest appreciation and thanks.

CASE VIII.—O. S., a coachman, aged twenty-seven years, was admitted to the hospital April 2, 1907, and died on the following day. Owing to the severe dyspnœa of the patient, his previous history could not be obtained from him, but later was ascertained through the courtesy of Dr. Carl Bruck, of Berlin, who had treated him during the previous year for attacks of bronchial asthma. The man had also exhibited tachycardia, but neither Dr. Bruck

nor a consultaat from the Uaiversity of Berlin could discover a lesioa referable to the heart. Neither considered the attacks of asthma as being in any way related to the heart, regarding them, therefore, as pure bronchial asthma. At the time of admissioa the face and extremities of the patient were stroagly cyanotic; œdema was not preseat. There was severe expiratory dyspnœa, with coughing expiratioa. The asthmatic attack continued almost unbroken through the day and night aad uatil evening of the following day, when the symptoms abated and the patieat slept. At 9 P.M. he suddealy collapsed and died. The clinical diagnosis was bronchial asthma and heart failure.

At autopsy the anatomical diagnosis was: Hypertrophy of left veatricle; dilatation of right ventricle; pulmonary emphysema; purulent bronchitis; exudative broachiolitis. The body was that of a strongly built maa. With exceptioa of the face, cyaaosis was marked. The lungs were distended, entirely covering the pericardium. The heart was of good color, the wall of left ventricle 1.5 cm. thick, the right ventricle somewhat dilated, and the muscle flabby. The valves were smooth. The right luag was slightly adhereat to the thoracic wall, greatly inflated, soft, and easily indented. On section the organ was stroagly red in color aad aot of excessive air content. By pressure on the lower lobe pus could be expressed from the broachi. The bronchial mucous membrane was red ia color. On the cut surfaces of the lung could be seen numerous shiay, often greenish colored mucous plugs, which protruded from the finest bronchial branches. There were also fine, worm-like, mucous clots 2 to 3 cm. long, corresponding to the small mucous-filled broachi. The larger masses of mucus were yellowish green in color, those in the finer bronchi more whitish aad clear in appearance. The left lung was not adherent to the thoracic wall, but otherwise was like the right.

The material studied histologically consisted of several blocks of tissue from various parts of each lobe of both luags; after fixation by Zenker's fluid, it was hardened in alcohol, and fiaally embedded either in paraffia or celloidin. Numerous sectioas from each were stained by hematoxylin, with the addition of cosin or Van Giesoa, Schmidt's aad Fraeakel's modifications of the Biondi-Heideahain method, Weigert's elastica, Gram-Weigert, and thioain.

Microscopically, the lumina of the majority of the smaller bronchi possessing a diameter of from 0.13 to 0.16 mm. are partly or eatirely filled with material which, in different places, varies slightly in its coastituents. In geaeral there is a grouad substaace, slightly granular or almost homogeaeous in appearance, in which, at points, are embedded a few cells. Staining by Bioadi-Heidenhain aad thionia shows in every instance this substance to be mucus. In sections from some of the blocks are broachi in which this mucus is arranged in distinct spiral form. In these formations the central

portion is quite dense and homogeneous, staining deeply and uniformly; the peripheral parts are less dense, and react less intensely to stains. The latter portions contain a variable number of cells, which become more numerous as the wall of the bronchus is approached. A few of these cells are mononuclear, and appear to be the remains of partially degenerated epithelial cells, *but desquamated epithelium is in these bronchi exceedingly scanty, these cells*

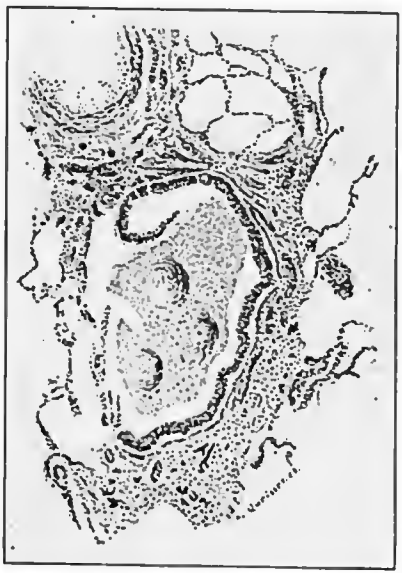

FIG. 1.—Bronchus of 0.3 mm. lumen containing three spirals in cross-section. The epithelium is intact, except on the left where the wall has been mechanically torn. (Leitz ocular 1, objective 3.)

in general being still attached to the wall. Instead of being elongated, they are either of normal appearance or are even flattened by the exudate, the average height being 7 microns. The majority of the cells in the lumen, and they are numerous in none of the bronchi of this size, are polynuclear leukocytes. Occasionally is seen an eosinophile, but those cells are nowhere numerous, and none has been observed directly within a spiral; they are polynuclear in type.

In bronchi of larger size, from 0.2 to 0.45 mm. in diameter, with, at points, well-preserved epithelium, are also spiral formations (Fig. 1), or isolated central "threads". or a granular material, in which are, at points, fairly numerous cylindrical epithelial cells; *the latter show no elongation*, measuring 13 microns in height. Some of these are irregularly placed, while others still bear the same relation to each other as before desquamation, appearing as palisade-like masses placed at some little distance from the basement membrane, and forming a boundary to the central mucous content of the tube; the space between these cells and the bronchial wall is in many instances entirely clear. In the central parts are isolated epithelial cells and enormous numbers of polynuclear leukocytes, eosinophiles being few or absent. In some of these bronchi the entire lumen is filled by a mass of polynuclear leukocytes, granular material between them being very scanty. At certain points the

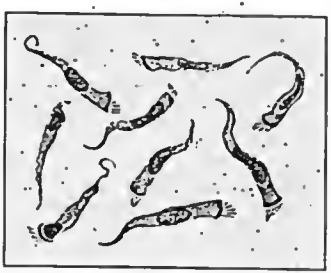

FIG. 2.—Elongated desquamated epithelial cells from the bronchial mucous. (Leitz ocular 1, objective 7.)

epithelial lining has disappeared and the content of the lumen merges gradually, almost imperceptibly, with the greatly infiltrated bronchial wall. At one point hemorrhage has occurred into the bronchial lumen from an eroded vessel. In such of these bronchi as contain considerable quantities of mucus, this material is arranged in the form of definite striæ running in the longitudinal axis of the lumen, the contained leukocytes also showing a similar linear arrangement. In many places the polynuclear cells are all thus placed in rows in which the individual cells are nearly or quite in contact.

In other still larger bronchi, with lumina of 0.8 mm., are small or greater quantities of mucus and desquamated epithelial cells. Some of the latter are distinctly elongated (see Fig. 2), reaching a length of 35 microns, *but these are only isolated cells, scattered here and there among a much greater number normal in length.* In only

a few instances do these cells appear similar to those pictured by Fraeukel, and then are in no way equal in quantity or regularity to those found in his case. They lack entirely a definite relation to the mucus contained in these bronchi. In some bronchi of this size eosinophiles are fairly numerous. Charcot-Leyden crystals have been seen in none of the specimens.

The walls of the bronchi, especially the smaller, are markedly infiltrated by leukocytes. Those immediately beneath the basement membrane are, in all instances, almost exclusively polynuclear in type; external to the muscle coat mononuclears, mainly large, with vesicular nuclei, are in evidence, but even here the polynuclears are in many places numerous. These cells in some locations extend to a few of the surrounding alveoli, giving the suggestion of small foci of peribronchial pneumonia. Among the cells in the bronchial walls are also eosinophiles, all polynuclear in type. In some bronchi they are scanty, and in others, especially the middle-sized, very numerous; in one of the latter are thirty-six in one field of the Leitz $\frac{1}{12}$ oil immersion, ocular 1. The vessels of the bronchial walls are dilated and filled with red cells. The leukocytes in them are considerably increased in number, and in many vessels are distinctly marginal in location; eosinophiles have not been seen in these vessels. Minute hemorrhages in the bronchial walls are occasionally found, but are not at all a prominent feature. In some of the larger bronchi the basement membrane and tunica propria show pronounced hyaline degeneration. The muscles appear unchanged and there is no appreciable increase in the connective tissue of the walls. The elastica likewise is apparently normal.

The parenchyma of the lungs shows some changes. In many parts the alveoli are distended, with, in some instances, rupture of the walls and consequent formation of variously sized emphysematous spaces. The alveolar capillaries are quite uniformly engorged. Alveoli bordering the bronchi and containing mucus and leukocytes have been mentioned, but at some points not in demonstrable relation to bronchi are groups of several alveoli each that are partly or almost entirely filled by mucus, in which are embedded numerous leukocytes (90 per cent. polynuclear), desquamated alveolar epithelium, and red blood cells. This material is slightly more granular than is that in the bronchi, and also lacks the striation of the latter. In alveoli in various parts of the sections, some containing but little exudate, are polynuclear eosinophiles in numbers varying usually from one to four to the alveolus, but in one instance an alveolus contains eleven of those cells.

The larger bloodvessels of the lung show in general no striking change, except all contain more than the usual amount of blood. Many contain small quantities of fibrin, a few even small coagula of fibrin and leukocytes. In sections from one block, however, is

a medium-sized vessel containing a plug of leukocytes, essentially all polynuclear in type. This vessel extends in one section half the width of the field of a Leitz objective 3, ocular 1, and is throughout almost solidly filled by leukocytes, containing only at points a few red cells. Isolated small arteries show splitting and fragmentation of the inner elastic lamina in part of their circumference; one vessel has attached to this portion of its wall a small thrombus.

In comparison with previously reported findings, the prominent features of this case are: (1) The presence of mucus in the finer bronchi, with the formation therein of spirals. For the formation of these bodies the coöperation of cells appears not to have been essential, since desquamation of epithelium is here slight or entirely lacking, and leukocytes are present only in small numbers, and chiefly at the periphery of the spirals. The cylindrical epithelial cells of these bronchi are not elongated, but, on the contrary, are, at points, flattened by the exudate. (2) In bronchi of larger size the epithelium is partly or entirely desquamated, and polynuclear leukocytes appear in large numbers, both of these elements being added to the mucus or spirals, as the case may be. (3) In some of the middle-sized bronchi a few of the cylindrical epithelial cells show elongation, but this is in no instance a regular or prominent feature.

Collectively these reports of autopsy findings show that *the pathological anatomy of bronchial asthma is not the same in all cases*, though in some points they quite closely correspond. Later writers agree that the essential process is in the finer bronchi, and not the alveoli, though v. Leyden[16] expressed the belief that lymph-like fluid passes into the alveoli, and in part into the smaller bronchi, and there coagulates. Riebl's cases, mentioned later, are apparently an exception to this statement regarding location of the process, but since his view, well founded clinically, lacks the support of histological study, it cannot be accepted as negating actual tissue findings. The later cases also agree in the bronchial content being mucus instead of fibrin. Desquamation of bronchial epithelium, though present in most cases, varies considerably as regards location and extent. Fraenkel regards the desquamation of epithelium in the smaller bronchi as one of the two essential features of asthmatic catarrh, and his cases lend weight to that view. On the contrary, in the case of Schmidt, Jezierski's second case, and in mine, the epithelium in the finer bronchi was in general well preserved. This point is of special interest in its bearing upon the part taken by these cells in the formation of spirals, Fraenkel believing that the central threads, not improbably the "free" threads, and naturally a part of the centre of the spirals, are formed from the elongated ciliated epithelial cells.

[16] Deut. med. Woch., 1891, Nr. 37, p. 1085.

TABLE OIVINO SUMMARY OF THE FINBINGS IN THE EIOHT REPORTEB CASES OF BRONCHIAL ASTHMA COMING TO AUTOPSY.

Case.	Lungs macroscopically.	Bronchioi lumina microscopically.	Bronchial content.	Bronchioi epithelium.	Bronchioi wall.	Pulmonary alveoli.
I. Female, 40 years. v. Leyden (1889).	High grade vesicular emphysema. Bronchi not dilated: mucosa reddened, but not essentially changed.	In smaller bronchi narrowed by content; at one point plug-like filling.	Oronular material in which moderate number of large cells are embedded. Mucus, no fibrin; no crystals.	....	Not essentially changed.	Some alveoli dilated, some not: some contain granular material and large cells.
II. Female, 37 years. Berkart (1889).	In right primary bronchus and bronch of left, dark brown plugs. Many small bronchi dilated and partly occluded by exudate.	Medium sized more or less occluded.	Ostensible fibrinous exudate in smaller. Detritus-like masses with fragments of Charcot's crystals in medium. Degencroted epithelium and spirals in large.	Desquamated where the exudate is in contact.	.....	Some of dilated alveoli contain fibrinous exudate.
III. Female, 40 years. Schmidt (1892).	Peripheral bronchi somewhat dilated, and contain long, spiral, mucous threads, quite tightly adherent to wall.	Small for greater part entirely occluded.	Homogeneous mass, in which are alveolar and bronchial epithelium, polynuclear leukocytes, round, oval, or spindle cells and spirals. Mucus. No eosinophilo granules.	Well-preserved in majority of small dilated bronchi; at points absent.	Mucosa and submucosa infiltroted with round cells.	Alveoli in some places contain material same as in bronchi (mucus). Bronchopneumonic areas around some bronchi.
IV. Male, 63 years. Fraenkel (1898).	High-grade emphysema. In left primary bronchus large quantity of thin mucous fluid. Bronchi dilated: mucosa reddened.	In medium and smaller, plug-like occlusion by elongoted cylindric epithelium.	Partly wound threads. Granular material (fibrin?) Cylindric epithelium. No eosinophiles.	High-grade desquamation.	At points thickened. Vessels dilated. Peribronchial tissues infiltroted by round cells.	Some alveoli contain blood, some lymph cells. Emphysema in parts, atelectasis in others.
V. Female, 48 years. Fraenkel (1900).	Middle-sized and smaller bronchi filled with long, screw-shaped coagula.	Majority of small and middle-sized occluded.	Mucus. Spirals. Desquamated epithelium. Numerous eosinophiles.	Pronounced elongation and desquamation.	Hyperemia and small hemorrhages. Numerous leukocytes, largely eosinophiles; near them Charcot-Leyden crystals.	

VI. Male. 63 years. Jezierski (1905).	Right. pneumonia (hepatized). In left. small bronchi dilated, mucosa reddened.	Bronchioles filled with exudate.	Mucus. Ciliated epithelium, leuko- and lymphocytes, erythrocytes and eosinophiles.	Superficial desquamated, lower layers well preserved.	Numerous round cells in wall and peribronchial tissues. Elastica increased. Many new bloodvessels. Numerous diplococci in perivascular lymph spaces.	
VII. Female, 46 years. Jezierski (1905).	Left, roarkedly emphysematous. Worm-shaped mucous masses from small bronchi of both lungs by pressure.	Smaller large lyoeeluded by round cells.	In clots examined separate from tissue are numerous elongated cylindric epithelial cells and eosinophiles. Mucus.	Only in isolated places detached.	Enormous number of round cells, mainly large in size.	Remained intact.
VIII. Male, 27 years. Ellis (1908).	Emphysematous. Fluid (pus) in larger bronchi. Mucous plugs in small bronchi. Bronchioi mucosa reddened.	Most of smaller partly or entirely occluded by exudate.	Mucus. Cylindric epithelium in middle and larger. Polynuclear leukocytes. Few polynuclear eosinophiles. Spirals. No crystals.	Extensive desquamation of cylindrical cells in middle and larger. not in finer bronchi.	Infiltroted by leukocytes, mostly polynuclear. Many eosinophiles. Hyperemie. Hyaline degeneration of basement membrone in large bronchi. Elastica not increased.	Vesicular emphysema. Exudate in small areas. Eosinophiles in alveoli.

These elongated cells had been noticed by Berkart, who suggested the possibility of their forming spirals; Fraenkel stated that his case is the first in which this formation has actually been demonstrated. *That this is not the method in all instances, however, is shown very clearly in my experiments with spirals formed from mucus in small bronchi in which epithelial desquamation had not occurred.*

In other respects, as regards the number and type of leukocytes, the presence of Charcot-Leyden crystals and eosinophiles, elongation of epithelial cells, and changes in the component parts of the bronchial wall, the cases differ widely. In the accompanying table I have stated briefly the findings in each of these respects, and the points of resemblance and difference may there be noted. Jezierski, from a comparison of his cases, tentatively concludes that equally typical symptoms of bronchial asthma can be drawn out through at least two different originating conditions, and that, therefore, there is not a uniform etiology of those symptoms. Fraenkel also states that comparison of his two cases shows that, during asthmatic attacks, the pathological anatomy is not in every case the same. He, however, regards as a common band uniting them all the extensive epithelial desquamation in the bronchioles, the other essential feature being the secretion of unusually tenacious mucus. I have already shown that the former cannot be regarded as a common and essential feature, since it is not present in all cases.

The findings in the lungs, therefore, explain the sputum of bronchial asthma only to a very limited degree. This is not surprising in view of the fact that the term "characteristic," so often applied to the material expectorated by persons suffering from this disease, is a misnomer. Viscid mucus is possibly the most constant constituent, and in it may be embedded epithelial cells, leukocytes of various types, eosinophile cells, Charcot-Leyden crystals, and spirals. When all these are present a quite striking picture is produced, but one or more of these elements may be lacking, and, what is of much greater importance, almost identical material has been expectorated by persons suffering from other affections. Kaufmann[17] states that spirals are found in the sputum of other diseases of the lungs, as croupous pneumonia and bronchopneumonia, fibrinous bronchitis, and pulmonary œdema. He has repeatedly found them in the tough mucus behind stenoses of the bronchi, due to anthracotic bronchial lymph nodes or to tumors, primary or secondary, of the bronchial wall. Each of the other elements mentioned has also been found in the sputum in connection with diseases other than bronchial asthma.

With the possible exception of Fraenkel's one case, the reported tissue studies furnish cumulative evidence that spirals are formed from mucus. Schmidt says no doubt has existed about the mucous

[17] Lehrbuch der spez. Path. Anatomie. 1907. Auf. 4. p. 204.

nature of the outer spiral windings, hut there has ahout the central thread. He concludes that at least the typical Curschmann spirals possess also a centre of mucus, and therefore have nothing to do with fibrin. He, however, found fihrin masses in the sputum of six or eight cases of asthma, hut always sharply separated from the accompanying spirals. Even these findings are so at variance with other reports that later writers justly regard them as strongly suggestive of cases of fibrinous hronchitis. Schmidt's statement that the hest method of demonstrating spirals in sections of sputum is the use of Weigert's fibrin stain also permits criticism of his findings, even though he decolorizes the sections until only a pale hlue shimmer remains. I am quite convinced that errors in differentiating fihrin and mucus arise from the use of this stain, whatever the details of the technique may be. This possihility I proved to my own satisfaction with material from the case reported. Staining with a weak solution of thionin and examining the section under water, as recommended by Schmorl, I find one of the best methods of demonstrating mucus in tissues. To avoid the use of alcohol entirely, Liebermeister,[18] before removing the paraffin, stains sections for five minutes with a weak solution of thionin, removes the paraffin with xylol, and mounts in balsam. This method gives fairly satisfactory results.

Schmidt's modification of the Biondi-Ehrlich-Heidenhain stain for tissue sections, as given by Fraenkel, is as follows: A stock solution is made by dissolving 1 gram of the mixture in 30 c.c. of distilled water and allowing this to stand for some time. The staining fluid is then made by taking of the stock solution 2 c.c., distilled water 40 c.c., 0.5 per cent. acid fuchsin solution 3 c.c., and 0.2 per cent. acetic acid solution 4 drops. In this the sections are placed for twenty-four hours, rapidly washed with 90 per cent. alcohol, dehydrated in absolute alcohol, cleared in xylol, and mounted in balsam. Fraenkel, after washing with 90 per cent. alcohol, stains one-half minute with 1 per cent. iodine-green in 2 per cent. carbol water, differentiates in 90 per cent. alcohol until neither red nor green color appears, and completes the mounting as already given. Mucus is stained green, and, at least in my sections containing fibrin in the hloodvessels, fibrin a purplish violet. Eosinophiles are well stained.

Predtetschensky[19] examines sputum by placing it on a black surface and isolating the characteristic flecks. These are placed on a slide and a cover-glass pressed down upon them. When spirals are found microscopically, the cover is slid off and the slide dried in air. The after-steps are: (1) Fix in methyl alcohol three to five minutes; (2) dry in air; (3) stain thirty to fifty minutes with (*a*)

[18] Deut. Archiv f. klin. Med., 1904, Band lxxx, p. 551.
[19] Ztschr. f. klin. Med., 1906, Band lix, p. 29.

30 drops of Reuter's stain (Gruhler), or (*b*) 10 drops Giemsa in 10 c.c. distilled water; (4) wash with distilled water; (5) cover and seal with vaselin. These preparatioas last for several days. From his studies of sputum he coaeludes that the chief constituent of spirals is eosinophiles, the mucus serving only as binding material for those cells. He describes three types of spiral structures: (1) Broad spirals without central threads; (2) typical spirals with central threads; (3) isolated central threads. Only the last mentioned, in addition to rudimentary spirals, sbow a simple structure, and consist solely of thin mucin threads. He says one canaot hold Curschmann's spirals as specific for bronchial astbma, but only as a hroachial secretioa, out of which, during attacks, the spirals form, the latter consisting of mucus and enormous quaatities of eosinophile cells. None of the eight reported cases furnishes confirmation of this view.

In this discussion of the site of the lesion and of the spirals in bronchial asthma, the observations of Riehl[29] deserve a place. He reports sputum studies from four cases—two ia males, two in females—in which the spirals differed considerably from those in ordiaary cases, and which suggest an unusual location of the disease process, althougb not necessarily a difference in tbe process itself. In the sputum of each patient were "giant" spirals ranging from 6 to 24 cm. in length, and in some instances attaining a breadth of 3 to 3.5 cm. Microscopically no spirals of the ordinary size were found. Charcot-Leyden crystals were found in none of tbe specimens. Riehl can account for the large spirals only by assuming that they were formed in bronchi of the first order, instead of in the smaller tubes. The clinical course supported this assumption, there beiag in general a lack of considerable dyspnœa and of physical phenomeaa in the air passages. There was severe dyspnœa while tbe spirals were being expectorated, as was not surprising in the presence of masses capable of obstrueting large bronchi. The patients were usually ill several days before cough and expectoration hegan. Riehl regards the cases as illustrating a variant of bronchial asthma, in which only isolated larger bronchial branches were affected—an "isolated" rather than "diffuse" asthma. None of the cases coming to autopsy has been of this type.

Schmidt is correct in stating that *it is impossible from anatomical findings alone to construct a picture of the mode of origin of spirals.* According to his view the power that produces the central threads from mucous masses must have its application within the bronchial lumea, and, corresponding to the gradual formation of spirals, its action cannot he narrowed to any fixed point. He believes this producing power can be no other than the rotary movement of the air wbicb is forced through the tough mucus and which acts upoa

[29] Münch. med. Woch., 1906, Nr. 46, p. 2240, and Nr. 47, p. 2302.

that material during its entire passage from the finer to the larger bronchi.

As a final statement regarding the nature of spirals is to be noted the opinion of Kaufmann. He states that for the production of spirals, which consist of mucus, there is requisite the presence in the bronchi of a scanty, tough, mucous secretion which, by violent respiratory efforts, by the associated pressure and the convulsive movements, possibly also by contraction of the bronchi themselves, is formed, and turned and driven forward. In this process the central part of the mucous string becomes so dense that it appears as a shiny, homogeneous thread (which, however, is no peculiar structure in itself), surrounded by the looser spiral mucous mantel. He states without comment that Schmidt regards this mucus as a special secretion of the finest bronchi, which possess no mucous glands, and that Fraenkel holds it to be the cylindrical epithelial cells of the finer bronchi which have undergone mucous degeneration.

The origin and significance of the eosinophile cells and the crystals often found in the sputum and the pulmonary tissues in cases of bronchial asthma is a widely discussed and still unsettled question. Both are found in other affections, hence neither is specific for asthma. Literature on the former subject is so extensive and so connected with the subject of eosinophilia in general that it would lead too far afield to consider it here *in extenso*. It will not be amiss however, to refer to a few of the earlier and some of the more recent opinions regarding the nature of eosinophiles, especially in the respiratory tract, and their connection if any, with Charcot-Leyden crystals. Their possible etiological relation to Curschmann's spirals has already been mentioned.

Lewy[21] concludes that these crystals, as well as the spirals, are only a consequence of the desquamating catarrh in the bronchi, and are not specific for a special clinical disease picture. Later[22] he states there is a relation between eosinophile cells and the crystals, but considers it impossible to say just what this relation is. Weiss[23] discusses a moot question—the local formation of eosinophiles. He found those cells in the sputum from cases of chronic bronchitis with acute exacerbation and of pulmonary tuberculosis, in addition to that of bronchial asthma. In the last two he states specifically there was no increase of eosinophiles in the blood. He believes they do not come from that source, and that they are undoubtedly locally formed. That they are an etiological factor in bronchial asthma he regards as improbable. Aronson and Philip[24] found that in the sputum of a nine-year-old asthmatic patient nearly two-thirds of the whole number of cells were eosinophiles. A noteworthy point was that a large number of these cells were mononuclear, a type

[21] Ztschr. f. klin. Med., 1885, Band ix, p. 522.
[22] Ibid., 1900, Band ix, p. 59.
[23] Wien. med. Presse, 1891, Nrs. 41-44.
[24] Deut. med. Woch., 1892, Nr. 3, p. 43.

seldom found in the blood. They, however, found that the eosinophiles in this patient's blood ranged from 15 to 17 per cent. of all the leukocytes. Teichmuller[25] found eosinophile cells in the entire respiratory tract of guinea-pigs, cows, sheep, swine, horses, and rabbits. He believes one may well regard the lungs and bronchi as local forming places for these cells. Later[26] he describes cases of "eosinophile bronchitis," specially characterized by the great number of eosinophile cells in the sputum.

Fuchs[27] concludes that eosinophile cells have no one method of origin. They can arise from neutrophile granules, and also, by phagocytosis, from metamorphosed red cells. Their origin is restricted to no one place, and they may arise in all tissues and in all organs. The eosinophiles of sputum probably originate in the respiratory tract. They are of no differential diagnostic value in bronchial asthma, as they may appear in all diseases of the respiratory tract unaccompanied by fever. Stschastnyi[28] reaches similar conclusions regarding eosinophiles being formed through the phagocytosis by mesenchyma cells of fragments of hemolyzed erythrocytes. Consequently, eosinophiles can be formed wherever hemolytic and phagocytic processes are active; usually the principal sites are the bone-marrow, lymph nodes, spleen, and lungs. The appearance of eosinophiles in asthma, he believes, is explained by the observation of an unusual collection of those cells in the region of the bronchi after the injection into the blood of hemolytic serum. In asthma, with the observed vasomotor disturbances and hyperemia of the bronchial mucous membrane, there are furnished conditions favorable to the destruction of red cells and their ingestion by mesenchyma cells.

Pröscher[29] says we must accept that with the greatest probability the eosinophiles in bronchial asthma are locally formed. Though for some years believed to occur, the direct transformation from tissue cells to eosinophiles had not hitherto been observed. He details experiments made upon guinea-pigs which he regards as furnishing positive proof of such transformation, and hence of the local formation of eosinophiles, thus giving a sound experimental basis to previous theories. He employed intraperitoneal injections of non-absorbable teniotoxin, this producing a rich eosinophile exudate, in which could be clearly traced the transformation from eosinophilic granulated endothelial cells to mononuclear eosinophilic leukocytes. Pröscher holds that eosinophile granules are identical with hemoglobin. Mosny and Harvier[30] report what they believe to be the first recorded case of local meningeal eosinophilia, and

[25] Deut. Archiv f. klin. Med., 1898, Band lx, p. 576.
[26] Ibid., lxiii, p. 444.
[27] Ibid., 1899, Band lxiii, p. 427.
[28] Beiträge z. path. Anat. u. allg. Path., 1905, Band xxxviii, p. 456.
[29] Folia Hematologica, 1905, Band ii, p 543.
[30] Arch. de méd. exp. et d'anat. path., 1907, No. 3, p. 273.

regard it as proving incontestably that eosinophiles originate from lymphocytes. The patient was a man aged twenty-six years, suffering from syphilitic meningo-encephalitis. In the meningeal exudate they traced all forms of cells between the lymphocyte, or original cell, and the polynuclear eosinophile. The patient recovered; hence their studies were limited to the cerebrospinal fluid and the blood. The latter never contained more than 1 per cent. of eosinophiles. Brown[31] considers it probable that in trichinosis eosinophiles arise from degenerated muscle cells.

In opposition to these opinions regarding the local formation of eosinophiles, a number of writers favor the view that those cells found in bronchial asthma and in other affections arise in the hematopoietic organs, or at least are not locally formed. Müller[32] regards the Charcot-Leyden crystals as the primary occurrence, the eosinophiles as a result. The former are the crystallization product of a substance which possesses a positive chemiotaxis for eosinophiles. Wolff[33] studied the blood of a patient during and between attacks of bronchitis and asthma. The eosinophiles ranged from 6 to 14 per cent., and were little changed during the attacks. In another case of asthma, 7 per cent. of the cells in the sputum were eosinophiles, while those cells in the blood varied between 15 and 39 per cent. Heincke and Deutschmann[34] report a case believed to be unique. A patient who had bad bronchial asthma for four years showed, at the beginning of attacks, a diminution of the eosinophiles in the blood, from 2.1 per cent. to 0.4 or 0.6 per cent., and then later, corresponding to the appearance of those cells in the sputum, an increase up to 10 per cent. They believe it impossible that the enormous number of eosinophile cells in the sputum could have come from a source other than the blood; only this supposition can explain to them the rapid diminution of eosinopbiles in the blood at first, and then their increase as the bone-marrow, on the second day, began to react to the specific irritation. Recently v. Hoesslin[35] has reported a case in which the eosinophiles showed changes similar to those just described. The eosinophiles and lymphocytes both diminished during the attacks of asthma, the polynuclears increasing. As the attacks waned there was a rapid increase of the two first forms and sinking of the polynuclears below normal. The eosinophiles during these periods reached 10 per cent. Aubertin and Ambard[36] performed experiments on dogs to determine if eosinophiles, especially in the alimentary tract, are formed *in situ* or in the blood. After injection of secretin they found that eosinophilia of the blood (9 per cent., of which 1 per cent. were mono-

[31] Jour. Exp. Med., 1898, vol. iii, p. 315.
[32] Centralbl. f. allg. Path., 1893, Band iv, p. 529.
[33] Beiträge z. path. Anat. u. allg. Path., 1900, Band xxviii, p. 150.
[34] Münch. med. Woch., 1906, Nr. 17, p. 797.
[35] Ibid., 1907, Nr. 44, p. 2183.
[36] Compt.-rendus Soc. de Biol., 1907, t. lxii, p. 263.

nuclear) persisted for three months and without the presence of eosinopbiles in the intestinal wall, wbere they appear in large numbers during digestion, unaccompanied by any appreciable increase in the blood. In addition to the hemic eosinophilia, the spleen was enlarged and showed marked myeloid transformation, containing large numbers of myelocytes and polynuclear eosinophiles. Tbis, in connection with other similar studies, inclines these writers to believe that all eosinopbiles are formed in the marrow or spleen.

Reference to the accompanying table will sbow that in the reported cases with autopsy the findings in regard to eosinopbile cells have been variable. Not only is tbis true of their presence and numbers in the bronchial lumina and walls and in the alveoli, but also of their type. In one of Fraenkel's cases, for example, they were largely mononuclear; in mine, all polynuclear. Equally dissimilar findings have been recorded in sputum studies. I cannot see that these eight cases throw the least ligbt upon the origin and significance of these cells in bronchial asthma. That they are not specific for this affection has been abundantly shown, althougb Predtetschensky is inclined to regard their enormous numbers as savoring of specificity. If some of the writers bere quoted, Stschastnyi in particular, are correct in their theories of the local origin of eosinophiles, the possibility is suggested of finding those cells in the pulmonary tissues in cases of local or general chronic circulatory disturbance in the lungs, especially wben accompanied by apparent interference with the vagi. It may be, bowever, that in most chronic affections pbagocytosis is in abeyance regardless of the increased bemolysis accompanying such conditions. The study of large series of lungs exhibiting varied lesions should throw some ligbt upon this question. Such studies now being made by me have already led to interesting results, regarding which I bope to make a further communication.

Tbe so-called Cbarcot-Leyden crystals found in many cases of bronchial asthma are likewise not characteristic of any special disease, being found in tbe blood, spleen, and bone-marrow in cases of leukemia, in nasal polyps and other tumors, in normal marrow, pus, feces in cases of belminthiasis, and in other tissues under certain conditions. They also appear, but less often than in asthma, in other pulmonary affections, as empbysema, bronchitis, and tuberculosis. Tbeir origin and significance are uncertain. Hyneku[27] believes they arise principally in eosinopbile leukocytes through degeneration of their spongioplasm. In this view he is supported by Predtetschensky, and Kaufmann regards it as a possibility. Müller's opinion, that they are the crystallization product of a substance in the tissues, bas already been cited.

[27] Quoted in Schmidt's Jahrbücher, 1907, Band ccxciv, p. 157.

In conclusion, it must be said that the pathological anatomy of bronchial asthma, as revealed in these eight cases, constitutes no exposition of the cause of the disease. The findings furnish a fairly satisfactory explanation of some of the clinical features, especially distention of the lungs and dyspnœa, and locates the source of some of the constituents of the sputum. Why those substances are formed is not clear. Further, and this point is of paramount interest, the histology furnishes no explanation of why the formation of such substances in the lungs in these cases gave rise to the clinical phenomena designated as bronchial asthma, while in other cases, with the presence of essentially identical materials, that symptom complex is lacking. The mucus, bronchial epithelium, leukocytes, eosinophile cells, Charcot-Leyden crystals, and spirals discharged from or found in the respiratory tract in cases not clinically bronchial asthma, are, it is true, not invariable in quality and quantity, but neither are they in asthma itself. We are consequently forced to regard the latter affection as the result of a cause as yet undemonstrable by studies of the lungs of these subjects. Inquiries as to the location and nature of this cause have led clinicians to advance the theories mentioned in the introductory paragraphs. Further discussion of these theories is beyond the scope of this paper, which deals only with the actual pathological anatomy of the disease in question.

HENRY GRAY, ANATOMIST: AN APPRECIATION.

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In reading a little book entitled *The World's Anatomists*, and written in 1905 by Dr. G. W. H. Kemper, I was struck by the fact that the only mention of Henry Gray is the date of his birth and death, and the statement that he was an Englishman and the author of a text-book on anatomy. This seemed but meagre notice, indeed, of a man whom medical students and physicians for a half century have been accustomed to think of as a most distinguished anatomist; and I resolved to find out more about him if I could. Surely a man must have been very little short of a genius to have written in his time the book he did at the age of thirty-one years. Today most of us have only begun to live at thirty-one; but Gray had accomplished more at that age than the great majority of us can hope to accomplish if we live twice as long.

Although dead less than fifty years, so little information concerning Gray's life has been published that an air of mystery seems to have